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RESEARCH ARTICLE

ATN blood biomarkers are related to digital cognitive assessment in type 1 diabetes

Luciana Mascarenhas Fonseca[1,2] | **Michal Schnaider Beeri**[3] | **Zoë W. Hawks**[4,5] | **Lanee Jung**[4,5] | **Michael Cleveland**[6] | **Nikki Delgado**[1] | **Jane Bulger**[7] | **Elizabeth Grinspoon**[4] | **Kamille Janess**[8] | **Martin J. Sliwinski**[9,10] | **Ruth S. Weinstock**[7] | **Jasmeer P. Chhatwal**[11,12] | **Pia Kivisäkk**[11] | **Laura Thi Germine**[4,5] | **Naomi S. Chaytor**[1]

[1]Elson S. Floyd College of Medicine, Washington State University, Spokane, Washington, USA

[2]Programa Terceira Idade (PROTER, Old Age Research Group), Department and Institute of Psychiatry, University of São Paulo School of Medicine, São Paulo, São Paulo, Brazil

[3]Herbert and Jacqueline Krieger Klein Alzheimer's Research Center, Rutgers University, New Brunswick, New Jersey, USA

[4]Institute for Technology in Psychiatry, McLean Hospital, Belmont, Massachusetts, USA

[5]Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, USA

[6]Department of Human Development, Washington State University, Pullman, Washington, USA

[7]Department of Medicine, SUNY Upstate Medical University, Syracuse, New York, USA

[8]Research Center and a Hospital, Jaeb Center for Health Research, Tampa, Florida, USA

[9]Department of Human Development and Family Studies, Pennsylvania State University, University Park, State College, Pennsylvania, USA

[10]Center for Health Aging, Pennsylvania State University, University Park, State College, Pennsylvania, USA

[11]Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

[12]Research Center and a Hospital, Brigham and Women's Hospital, Boston, Massachusetts, USA

Correspondence
Luciana Mascarenhas Fonseca, Department of Community and Behavioral Health, Elson S. Floyd College of Medicine, Washington State University, 665 N. Riverpoint Blvd, Office 456, Spokane, WA 99202, USA.
Email: luciana.fonseca@wsu.edu

Laura Thi Germine and Naomi S. Chaytor are co-senior authors.

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Abstract

INTRODUCTION: Associations between amyloid-tau-neurodegeneration (ATN) plasma biomarkers and cognition have not been characterized in adults with type 1 diabetes (T1D).

METHODS: Using data from participants in the Glycemic Variability and Fluctuations in Cognitive Status in Adults with T1D (GluCog) study ($N = 114$), we evaluated associations between phosphorylated tau (pTau)181, pTau217, β-amyloid 42/40 ratio, glial fibrillary acidic protein (GFAP), and neurofilament light (NfL) and self-administered digital cognitive tests, adjusting for age, sex, education, comorbidities (e.g., kidney disease), and glycemic indices.

RESULTS: Higher concentrations of pTau181 and GFAP were associated with slower responses on working memory tasks (pTau181: $\beta = 0.261$; $p = 0.007$; GFAP: $\beta = 0.175$, $p = 0.036$), and higher β-amyloid 42/40 ratio was associated with better vocabulary ($\beta = 0.260$, $p = 0.009$).

Discussion: Digital cognitive performance was associated with several ATN plasma biomarkers in T1D adults. Prospective studies are needed to understand the utility of these biomarkers in T1D.

KEYWORDS
Alzheimer's disease, cognition, plasma biomarkers, type 1 diabetes

Highlights

- There is an increase in life expectancy for individuals with type 1 diabetes (T1D).
- Few studies investigate the relationship between T1D and neurodegeneration.
- We characterize the relation between ATN plasma biomarkers and cognitive function.
- Digital cognitive performance was associated with plasma biomarkers in T1D adults.

1 | INTRODUCTION

Recent years have seen a considerable rise in the number of individuals diagnosed with type 1 diabetes (T1D), along with an increase in life expectancy.[1] T1D is a chronic autoimmune disease characterized by the destruction of insulin-producing beta cells in the pancreas. Insulin is known to play a key role in regulating biochemical processes related to cognitive functioning,[2] Individuals with longstanding T1D accumulate risk factors for cognitive decline and Alzheimer's disease (AD) and related dementias (ADRD) including micro- and macrovascular disease, chronic hyperglycemia, and severe hypoglycemia.[3–5]

Evidence suggests that middle-aged individuals with T1D have elevated levels of cerebrospinal fluid (CSF) AD biomarkers,[6] and that older adults with T1D have an elevated risk of developing ADRD[7] compared to individuals without diabetes. A large body of research has demonstrated consistent associations of type 2 diabetes (T2D) with a greater risk of mild cognitive impairment (MCI) and ADRD.[8] However, there are fewer studies examining the relationships between T1D and neurodegeneration, and it remains unclear how much AD and tau pathology contribute to cognitive dysfunction in this population. A recent study using plasma β-amyloid 42/40, phosphorylated tau (ptau) 181, neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) found that higher concentrations of NfL and ptau181 were associated with declines in psychomotor and mental efficiency over 32 years measured using traditional neuropsychological tests.[9]

Recently, highly specific, and ultrasensitive assays for plasma biomarkers for neurodegenerative diseases have been developed.[10,11] However, the associations of such biomarkers with cognition vary across populations, and their concentrations are associated with various comorbidities including chronic kidney disease.[12,13] Due to the filtering of the blood by the kidneys, kidney disease may alter the concentrations of those biomarkers in plasma, decreasing their accuracy in predicting brain pathologies.[14–16] Although there is a higher incidence of kidney disease in those with T1D,[17,18] we have found no studies of the use of plasma assays for amyloid-tau-neurodegeneration (ATN) biomarkers in these individuals considering kidney disease.

This study aimed to characterize the relationships between ATN plasma biomarkers and cognitive function measured via digital assessment, after controlling for diabetes complications and vascular risk factors, including kidney disease and measures of glycemic control, in individuals with T1D.

2 | METHODS

2.1 | Study setting

2.1.1 | Study ethics

This study analyzed data from the Glycemic Variability and Fluctuations in Cognitive Status in Adults with Type 1 Diabetes (GluCog) Study. Written informed consent was obtained from all participants, and all study procedures were conducted in compliance with the Declaration of Helsinki. This study was approved by the Jaeb Center for Health Research Institutional Review Board.

2.1.2 | GluCog study

The GluCog Study aimed to investigate the relationship between glycemic excursions and cognitive functioning using digital cognitive assessment in adults with T1D. Four endocrinology centers participated in the study with central clinical site coordination by the Jaeb Center for Health Research. The design, implementation, and assessments have been described in more detail elsewhere.[19]

2.2 | Study sample

The analysis sample ($N = 114$) included adults with T1D (age range 19–84 years, mean = 48.9) and at least 1 year since diagnosis (range 1–56, mean = 28.4) who participated in the GluCog study and also provided

RESEARCH IN CONTEXT

1. **Systematic review**: With the availability of better diabetes treatment regimens, adults with type 1 diabetes (T1D) are living longer. This substantial increase in life expectancy is accompanied by age-related diseases, such as dementia. However, there are few studies examining the relationships between T1D, aging, and neurodegeneration. Relevant publications are appropriately cited.
2. **Interpretation**: Digital cognitive performance was associated with ATN plasma biomarkers in T1D adults. Associations between plasma biomarkers and cognitive function remained significant after further adjusting for kidney disease and other diabetes complications.
3. **Future directions**: Future studies are needed with larger, older, and more diverse samples to understand the utility of ATN plasma biomarkers in T1D. The possible effect of renal function on ATN biomarkers also requires further study, including estimated glomerular filtration rate (eGFR) and cerebrospinal fluid (CSF) or imaging biomarkers.

blood samples for plasma biomarker data. The exclusion criteria included significant visual, motor, or hearing impairment, or a medical condition that interfered with the completion of the study, severe chronic kidney disease (CKD, estimated glomerular filtration rate [eGFR] < 30 mL/min), and being unable to complete remote assessment between 9 a.m. and 9 p.m. None had a diagnosis of dementia.

2.3 | Data collection

2.3.1 | Baseline digital neuropsychological assessment

Cognition was assessed through a secure web application (TestMyBrain digital platform) to complete a battery of self-administered tests that took approximately 40 min.[20] Participants were instructed to complete the test in a quiet room in a single sitting. Tests were completed on a laptop, desktop, or tablet computer. The selection of neuropsychological tests was based on the psychometric characteristics and recommendations from the Core Neuropsychological Measures for Diabetes and Obesity Trials.[21] The tests included: *Verbal and nonverbal reasoning*: (1) TestMyBrain (TMB) Vocabulary[22,23] and (2) TMB Matrix Reasoning;[23,24] *Memory*: (3) TMB Visual Paired Associates Memory;[24] *Working memory*: (4) TMB Flicker Change Detection,[19] (5) TMB Multiple Object Tracking (MOT),[25] and (6) TMB Paced Serial Addition Test (PSAT);[19] *Cognitive control/executive functioning*: (7) TMB Gradual Onset Continuous Performance Test (GradCPT);[24] and (8) TMB Letter-Number Switching;[26] *Processing speed*: (9) TMB Digit Symbol Matching (DSM);[22–24] and *Psychomotor speed*: (10) TMB Simple Reaction Time,[24,27] and (11) TMB Choice Reaction Time (Choice RT).[24,27] These cognitive tasks are reliable, valid for remote digital administration,[28] and have been fully described elsewhere.[19] Measures of accuracy and median reaction time (RT) for correct responses for each test were computed as appropriate. For measures of accuracy, a higher score reflects better cognitive performance, while a longer RT indicates more difficulty responding to a stimulus.

2.3.2 | Plasma sampling and analysis

Whole blood for plasma sampling was collected within 6 months of the cognitive assessments in 10 mL ethylene-diamine-tetra-acetic (EDTA) hematology tubes and processed within 30 min of collection at each of the four endocrinology centers that participated in the study. Following centrifugation, the isolated plasma was divided into 250 microliter (μL) aliquots frozen within 30 min of centrifugation and stored at −80°C until performing the biomarker assays. Plasma β-amyloid 40 and 42, pTau181, NfL, and GFAP concentrations were measured in the Mass General Institute for Neurodegenerative Disease (MIND) Biomarker Core at Massachusetts General Hospital using the Quanterix Simoa Neurology 4-plex E (N4PE) and Tau181 immunoassays on a Quanterix HD-X fully automated analyzer, according to the manufacturer's protocols. Plasma tau phosphorylated at threonine 217 (pTau217) concentrations were measured using the AlzPath Simoa immunoassay in the Quanterix laboratory. All plasma biomarkers were run in duplicate, and values were averaged. Samples were retained for analysis if the coefficient of variation (CV) was < 20% across the duplicate measurements.

2.3.3 | Glycemic control

Hemoglobin A1c (HbA1c) was collected within 3 months of baseline at the clinic visit. Continuous glucose monitor (CGM) data were collected starting concomitantly with baseline assessment using a Dexcom G6 Professional CGM System (Dexcom CGM, Food and Drug Administration-approved) that was worn for up to 20 days (two sensors were provided with up to 10 days wear time). The CGM system consists of a sensor, a transmitter, and a receiver that measures interstitial glucose concentrations every 5 min. The CV of CGM readings was calculated as the ratio of the standard deviation to the mean. Participants were blinded to the study CGM readings; however, as the use of CGM is considered standard care for T1D, some participants used personal CGM devices in addition to the study-administered device.

2.3.4 | Diabetes characteristics, complications, and vascular risk factors

Information regarding age at T1D onset and diabetes duration, as well as diabetes-related complications, were retrieved via medical record

review. The presence of any of the following medical records was classified as "kidney disease": abnormal kidney function, microalbuminuria, renal impairment, kidney transplant, chronic kidney disease, and diabetic nephropathy. Several lifetime severe hypoglycemic events (an event requiring assistance with corrective actions to raise glucose) were self-reported.

2.3.5 | Other instruments and measures

Participants completed self-administered questionnaires for the collection of sociodemographic data. Sex was self-reported. Education was categorized as high school, technical school, some college, college degree, and graduate/professional degree. Race and ethnicity were self-reported. Body mass index (BMI) was calculated using height and weight assessments from the in-person clinic visit.

2.4 | Data treatment and statistical analysis

2.4.1 | Digital cognitive data quality control

Information about browser, screen size, and operating system were passively collected during digital cognitive data collection. They were considered for the interpretation of the cognitive data, as they may influence data quality.[29] Exclusion criteria when task performance was comparable to chance or unlikely to represent adequate effort can be found in Supplemental Material. This was rare (zero to six participants excluded per test).There were no associations between data quality and cognitive performance or plasma biomarkers ($p > 0.5$).

2.4.2 | CGM data quality

We excluded the first 24 h of data from the CGM device due to the reduced accuracy of data capture, consistent with the manufacturer's instructions.[30]

2.4.3 | Statistical analysis

The Shapiro–Wilk test was used to test for normality, and nonparametric analysis was used when needed. To determine whether cognitive tests were associated with concentrations of the five plasma biomarkers, we first performed bivariate correlation analyses using Spearman's rho, as the data did not follow a normal distribution. Relationships between biomarkers, demographics, and diabetes characteristics were evaluated using Spearman's rank correlation, Mann–Whitney U, and Kruskal–Wallis tests, as appropriate. To control for type 1 error, given multiple comparisons, we applied false discovery rate (FDR) corrections to *p*-values. Significant correlations between cognition and plasma biomarkers after FDR correction were re-analyzed using multiple linear regression, with the biomarker assigned as the outcome and cognitive function as the predictor in separate models, adjusting for age, sex, and education (Model 1). Except for the regressions of β-amyloid 42/40 (with TMB Vocabulary and T1D age diagnosis), model residuals were non-normally distributed. To satisfy regression assumptions of normally distributed residuals, pTau217, pTau181, NfL, and GFAP biomarkers were log10 transformed in final analyses. Models were built in stages to examine incremental variance explained (ΔR^2) by kidney diseases (Model 2) and other diabetes characteristics (Model 3). Specifically, we modeled other diabetes characteristics that were associated with the respective plasma biomarkers in the bivariate analysis. We also examined multicollinearity among independent variables. The alpha level for statistical significance was set at 0.05. Statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS), version 28 for Windows.

3 | RESULTS

3.1 | Participant characteristics

Table 1 reports participant demographic and diabetes characteristics, as well as the plasma biomarker concentrations. Table 2 presents neuropsychological performance on the digital measures. For each test, we provide measures of accuracy and median RT for correct responses, where appropriate.

3.2 | Associations between cognitive performance and plasma biomarkers

Table 3 shows the results of the correlation analyses to evaluate the associations between cognitive functions and plasma biomarkers with FDR-corrected *p*-values. We found that lower β-amyloid 42/40 was associated with worse TMB Vocabulary accuracy, and it was the only biomarker that correlated with this test. Higher pTau181 and pTau217 concentrations were associated with longer median RT for correct responses on 6 and 7 of 11 tests, respectively. Higher GFAP concentration was associated with lower accuracy on five of the tests and with longer median RT on eight tests. Higher NfL concentration was associated with lower accuracy on four tests and with longer median RT on eight tests.

3.3 | Associations between diabetes comorbidities, glycemic variability, and plasma ATN biomarkers

Adjusted linear regression models with the variables that were significantly correlated in bivariate analysis are shown in Table 4. Higher concentrations of pTau181 were associated with greater glycemic variability and higher likelihood of having kidney disease, while higher concentrations of pTau217 were associated with longer diabetes duration, higher likelihood of having neuropathy and kidney disease. Higher concentrations of NfL were associated with higher HbA1c and the

TABLE 1 Demographic and clinical characteristics of the participants

Parameter	Total sample $N = 114$
Age, mean (SD)/range ($n = 112$)	48.9 (14.4)/19–84 years
Female self-reported sex, *n* (%)	60 (52.6)
Education ($n = 108$), *n* (%)	
High school	6 (5.3)
Technical school	22 (19.3)
Some college	16 (14.0)
College degree	45 (39.5)
Graduate degree or more	22 (19.3)
Not sure or not reported	3 (2.6)
Ethnicity, *n* (%)	
Hispanic or Latinx	11 (9.6)
Not Hispanic or Latinx	103 (90.4)
Race, *n* (%)	
Asian	1 (0.9)
Black or African American	6 (5.3)
Multiracial	2 (1.8)
Native Hawaiian/Pacific Islander	1 (0.9)
Unknown	2 (1.8)
White	102 (89.5)
Age at T1D diagnosis, mean (SD)/range	20.2 (12.6)/1–57
Age at diagnosis ≤ 18 years (yes), *n* (%)	59 (51.8)
Diabetes duration, mean (SD)/range	28.47 (14.66)/1–56
BMI (kg/m^2), mean (SD)/range	28.46 (5.68)/18–45
CGM CV (%), mean (SD)/range	36.59 (7.28)/11.00–68.00
HbA1c (mmol/mol), mean (SD)/range	7.59 (1.32)/5.4–12.0
Severe hypoglycemic events (number of life events), mean (SD)/range	2.08 (2.26)/0.0–6.0
Diabetes complications (yes), *n* (%)	
Kidney disease[a]	10 (8.8)
Neuropathy	13 (11.4)
Retinopathy	5 (4.4)
Microvascular disease[b]	22 (19.3)
Vascular risk factors (yes), *n* (%)	
Hypertension	42 (36.8)
Hyperlipidemia	48 (42.1)
Plasma biomarkers (pg/mL), mean (SD)/range *(excluded those with CV > 25%)*	
pTau181 ($n = 104$)	2.49 (1.50)/0.69–7.23
pTau217 ($n = 114$)	0.43 (0.25)/0.13–1.29
β-amyloid 42/40 ($n = 112$)	0.067 (0.010)/0.041–0.094
GFAP, pg/mL ($n = 111$)	87.31 (49.81)/23.61–273.84
NfL, pg/mL ($n = 113$)	16.42 (10.51)/3.73–59.7

Abbreviations: BMI, body mass index, CGM, continuous glucose monitor; CV, coefficient of variation; GFAP, glial fibrillary acidic protein; HbA1c, hemoglobin A1c test; T1D, type 1 diabetes; NfL, neurofilament light chain; pTau, phosphorylated tau; SD, standard deviation.

[a]Kidney disease included any of the following by medical records: abnormal kidney function, diabetic nephropathy, microalbuminuria, renal impairment, kidney transplant, or chronic kidney disease.

[b]Presence of at least one microvascular complication.

presence of kidney disease. Lower β-amyloid 42/40 ratios were associated with older age of T1D onset, adult T1D onset, and shorter diabetes duration. After adjustments, GFAP was only associated with severe hypoglycemic events.

3.4 | Adjusted associations between cognitive function and ATN plasma biomarkers

Table 5 presents the results of separate linear regression models investigating the relationships between cognitive function and ATN plasma biomarkers that were significant when adjusting for age, sex, and education. Models were built in stages to evaluate variance explained by age, sex, and education (model 1, R^2), as well as incremental variance explained by kidney disease (model 1 vs. 2, ΔR^2a) and diabetes variables that were associated with each of the plasma biomarkers in Table 4 (model 2 vs. 3, ΔR^2b). Based on these analyses, we determined that longer TMB PSAT median RT was associated with higher concentrations of pTau181 (Model 1, $R^2 = 26\%$). The associations between TMB PSAT median RT and pTau181 remained significant after accounting for kidney disease (Model 2, ΔR^2a = 4.6%) and glycemic variability (Model 3, ΔR^2b = 4.9%). Higher GFAP concentrations were associated with slower TMB PSAT median RT, adjusting for age, sex, and education (Model 1, $R^2 = 40.7\%$). After adjusting for kidney disease (Model 2, ΔR^2a = 6.0%), the association between GFAP and TMB PSAT median RT was no longer significant. However, with the inclusion of the diabetes characteristic associated with GFAP in Table 4, GFAP was significantly associated with TMB PSAT median RT (Model 3, ΔR^2b = 8.0%). Furthermore, lower β-amyloid 42/40 ratios were associated with worse TMB Vocabulary accuracy (Model 1, $R^2 = 6.9\%$), and these associations persisted after accounting for kidney disease (Model 2, ΔR^2a = 0.00001%) and age at T1D diagnosis (Model 3, ΔR^2b = 9.2%).

TABLE 2 Baseline cognitive performance of the participants

Parameter	Total sample (*N* = 112)
Cognitive assessment	*Mean (SD)/range*
Verbal and nonverbal reasoning	
TMB Vocabulary Test[b]	
Accuracy, %	0.83 (0.09)/0.56–0.96
Median RT for a correct response, ms	3279 (764) / 2061 – 7071
TMB Matrix Reasoning[c]	
Accuracy, %	0.75 (0.09)/0.38–0.94
Median RT for a correct response, ms	5673 (2658)/2335–15224
Memory	
TMB Visual Paired Associates Memory[f]	
Accuracy, %	0.57 (0.18)/0.20–0.95
Median RT for a correct response, ms	3635 (1114)/1397–7214
Working memory	
TMB Flicker Change Detection[b]	
Accuracy, %	0.95 (0.06)/0.59–1.00
Median RT for a correct response, ms	5848 (2133)/2588–11921
TMB MOT[b] *Accuracy, %*	0.73 (0.10)/0.44–0.94
TMB PSAT[e]	
Accuracy, %	0.74 (0.15)/0.37–1.0
Median RT for a correct response, ms	822 (179)/387–1199
Cognitive control/executive function	
TMB GradCPT[b]	
Median RT for a correct response, ms	855 (92)/448–1014
d-prime[d]	2.48 (0.78)/0.61–4.21
TMB letter-number switching[b]	
Accuracy, %	0.96 (0.04)/0.68–1
Median RT for a correct response, ms	1252 (381)/599–2409
Processing speed	
TMB DSM[c]	
Median RT for a correct response, ms	1091 (339)/620–2466
Psychomotor speed	
TMB Simple Reaction Time *Median RT for a correct response, ms*	361 (81)/245–626
TMB Choice Reaction Time[a] *Accuracy, %*	0.97 (0.05)/0.60–1
Median RT for a correct response, ms	1024 (368)/631–3467

Abbreviations: DSM, Digit Symbol Matching; GradCPT, Gradual Onset Continuous Concentration Test; MOT, Multiple Object Tracking; ms, milliseconds; PSAT, Paced Serial Addition Test; RT, reaction time; SD, standard deviation; TMB, TestMyBrain.

[a] $n = 108$;.

[b] $n = 111$;.

[c] $n = 109$;.

[d] d-prime is a measure of discrimination sensitivity (accuracy).

[e] $n = 105$;.

[f] $n = 110$.

To clarify the influence of childhood versus adult T1D onset in the associations between β-amyloid 42/40 ratios and TMB Vocabulary accuracy, we re-ran β-amyloid 42/40 ratios analyses (Model 3) with age coded as a binary (≤ 18 years of age, > 18 years of age) rather than continuous variable. Associations between lower β-amyloid 42/40 ratios and worse TMB Vocabulary accuracy persisted ($\beta = 0.220$ $p = 0.024$). To further understand the impact of age at diagnosis, we conducted a secondary analysis examining age (continuous) as a moderator of associations between β-amyloid 42/40 ratios and TMB Vocabulary accuracy. Age at onset emerged as a significant moderator ($\beta = -0.304$, $p = 0.005$, $R^2 = 0.08$). Specifically, the positive association between β-amyloid 42/40 ratios and TMB Vocabulary accuracy was stronger in participants with older onset of T1D.

4 | DISCUSSION

In 114 adults with T1D, ATN plasma biomarkers correlated with tests from multiple cognitive domains in unadjusted bivariate analyses. Multivariate analyses, adjusting for demographics, further revealed that higher concentrations of pTau181 and GFAP were associated with slower working memory and lower β-amyloid 42/40 ratios were associated with worse verbal reasoning. The associations of cognition with pTau181, β-amyloid 42/40, and GFAP remained significant after further adjusting for the presence of kidney disease and other diabetes complications.

The fact that slower working memory, but not accuracy, was related to pTau181 and GFAP in this study suggests that working memory speed may be a sensitive early indicator of neurodegeneration in the T1D population. Our results are consistent with meta-analytic evidence linking longer RTs to MCI in the general population.[31,32] Working memory RT is not typically measured using traditional working memory tasks, raising the possibility that the digital assessment battery used in this study may have facilitated this finding. Given the relatively younger age of the sample, our findings may indicate that slower working memory performance precedes overt errors. However, it is also important to note that other RT measures used in this study were not associated with biomarkers in the final models.

Our results showed that having a lower plasma β-amyloid 42/40 ratio, a marker of AD pathology,[33] was associated with worse performance on a vocabulary test, a measure of crystallized cognitive ability. Verbal ability is known to resist the effects of non-pathological aging[34] and is related to the concept of cognitive reserve[35] in which cognitive abilities may serve as advantageous resources that delay the impacts of neuropathological degeneration. The associations found here suggest that people with less crystalized cognitive ability may be more prone to Alzheimer's pathology compared to those with more crystalized cognitive resources; however, this hypothesis needs to be confirmed.

Different concentrations of plasma biomarkers may indicate subtle differences in neuropathology and symptom onset, yet their importance in the cognitive status of adults with T1D remains unclear. In this study the associations between cognitive performance and pTau181, GFAP, and β-amyloid 42/40 ratio were all in the pathological direction.

TABLE 3 Unadjusted correlations between ATN biomarkers and performance in baseline cognitive assessment with *p*-values adjusted for multiple comparisons using FDR.

	ATN biomarker				
	Spearman's Rho				
Parameter	pTau181 ($n = 102$)	pTau217 ($n = 111$)	β-amyloid 42/40 ($n = 109$)	GFAP ($n = 108$)	NfL ($n = 110$)
Baseline cognitive assessment					
Verbal and nonverbal reasoning					
TMB Vocabulary					
Accuracy	0.111	0.029	0.272[a]	0.129	−0.026
Median RT for correct response	0.170	0.072	0.036	0.103	−0.29
TMB Matrix Reasoning					
Accuracy	−0.037	−0.095	−0.043	−0.102	−0.222[b]
Median RT for correct response	0.134	0.130	−0.021	0.269[a]	0.089
Memory					
TMB Visual Paired Associates Memory					
Accuracy	−0.120	−0.076	0.170	−0.245[a]	−0.159
Median RT for correct response	0.217[a]	0.254[b]	0.022	0.227[a]	0.226[a]
Working memory					
TMB Flicker Change Detection					
Accuracy	−0.125	−0.172	−0.010	−0.316[b]	0.307[b]
Median RT for correct response	0.247[a]	0.238[b]	0.019	0.437[b]	−0.395[b]
TMB MOT					
Correct responses	−0.148	−0.128	0.024	−0.342[b]	−0.234[b]
TMB PSAT					
Accuracy	−0.045	−0.111	0.078	−0.234[a]	−0.233
Median RT for correct response	0.393[b]	−0.255[a]	0.071	0.339[b]	0.275[b]
Cognitive control/executive functioning					
TMB GradCPT					
d-prime	−0.135	−0.113	0.114	−0.316[b]	−0.227[a]
Median RT for correct response	0.272[b]	0.256[b]	−0.044	0.474[b]	0.388[b]
TMB Letter-Number Switching					
Accuracy	0.106	0.130	0.074	−0.024	−0.062
Median RT for correct response	0.174	0.207[a]	−0.043	0.313[b]	0.294[b]
Processing speed					
TMB DSM					
Median RT for correct response	0.270[b]	0.391[b]	−0.046	0.386[b]	0.342[b]
Psychomotor speed					
TMB Simple Reaction Time					
Median RT for correct response	0.146	0.038	0.104	0.154	0.239[a]
TMB Choice Reaction Time Accuracy	0.004	−0.013	−0.020	−0.061	−0.090
Median RT for correct response	0.242[a]	0.231[a]	−0.082	0.429[b]	0.454[b]

Abbreviations: ATN, β-amyloid, tau pathology, and neurodegeneration; DSM, Digit Symbol Matching; FDR, false discovery rate; GFAP, glial fibrillary acidic protein; GradCPT, gradual onset continuous concentration test; MOT, Multiple Object Tracking; ms, milliseconds; PSAT, Paced Serial Addition Test; NfL, neurofilament light chain; pTau, phosphorylated tau; RT, reaction time; TMB, TestMyBrain.

[a]Correlation is significant at the 0.05 level (2-tailed) after FDR correction.

[b]Correlation is significant at the 0.01 level (2-tailed) after FDR correction.

TABLE 4 Separate linear regression models for the associations between ATN plasma biomarkers and diabetes characteristics that were first associated with the respective biomarker in bivariate analysis, adjusted for age, sex, and education

	Unstandardized coefficient	Standardized coefficient	95% confidence interval for *B*		
Parameter	*B*	*β*	Lower bound	Upper bound	*p*-value
Dependent variable: pTau181 (*n* = 102)					
Predictor: Glycemic variability	0.008	0.240	0.002	0.013	0.008
Diabetes duration	0.003	0.163	−0.001	0.007	0.158
Hypertension	0.044	0.089	−0.053	0.142	0.370
Hyperlipidemia	0.057	0.118	−0.041	0.155	0.254
Neuropathy	0.087	0.122	−0.040	0.214	0.177
Kidney disease[a]	0.201	0.251	0.062	0.339	0.005
Dependent variable: pTau217 (*n* = 114)					
Predictors:					
BMI	0.003	0.077	−0.003	0.010	0.343
Diabetes duration	0.004	0.249	0.001	0.007	0.012
Hypertension	0.034	0.071	−0.049	0.117	0.415
Hyperlipidemia	0.037	0.077	−0.047	0.120	0.388
Neuropathy	0.121	0.167	0.011	0.232	0.031
Kidney disease[a]	0.140	0.171	0.016	0.264	0.028
Dependent variable: *β*-amyloid 42/40 (*n* = 109)					
Predictor:					
T1D diagnosis age	−0.0003	−0.350	−0.0004	−0.0001	<0.001
Age at diagnosis ≤ 18 years	0.007	0.331	0.003	0.011	0.001
Diabetes duration	0.0003	0.407	0.0001	0.0004	<0.001
Dependent variable: GFAP (*n* = 108)					
Predictors:					
Diabetes duration	0.003	0.170	−0.0003	0.006	0.076
Hypertension	0.002	0.004	−0.78	0.082	0.962
Hyperlipidemia	0.028	0.062	−0.051	0.108	0.480
Severe hypoglycemic events	4.137	0.209	0.652	7.622	0.021
Dependent variable: NfL (*n* = 110)					
Predictors:					
T1D diagnosis age	−0.002	−0.096	−0.05	0.001	0.255
Diabetes duration	0.002	0.111	−0.001	0.005	0.255
HbA1c	0.055	0.286	0.028	0.083	<0.001
Hypertension	0.090	0.168	0.000	0.179	0.050
Hyperlipidemia	−0.017	−0.033	−0.108	0.073	0.706
Kidney disease[a]	0.193	0.215	0.062	0.324	0.004

Abbreviations: ATN, *β*-amyloid, tau pathology, and neurodegeneration; BMI, body mass index, GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; pTau, phosphorylated tau; T1D, type 1 diabetes.

[a]Kidney-related disease includes any of the following by medical records: abnormal kidney function, diabetic nephropathy, microalbuminuria, renal impairment, kidney transplant, or chronic kidney disease. Data for pTau181, pTau217, GFAP, and NfL were log10 transformed in the regression models.

The more pathological the concentrations of biomarkers of neurodegeneration, the worse the cognition in specific tasks in this adult sample of individuals with T1D with no diagnosis of dementia. GFAP, *β*-amyloid 42/40 ratio, and pTau181 are all associated with dementia.[36] However, GFAP is considered a nonspecific marker of neurodegeneration[37] associated with *β*-amyloid deposition but not with tau aggregation.[38] PTau181 is considered one of the best plasma biomarker predictors of in vivo amyloid beta deposition and cognitive decline[36] in the gen-

TABLE 5 Significant associations between cognitive performance and ATN plasma biomarkers in pairwise linear regression models adjusted for age, sex, and education (Model 1), and additionally for kidney disease (Model 2) and other diabetes characteristics associated with the respective biomarker (Model 3)

	Unstandardized coefficient	Standardized coefficient	95% confidence interval for *B*		
Parameter	*B*	*β*	Lower bound	Upper bound	*p*-value
Dependent variable: pTau181 (*n* = 96)					
Predictor: ***Working memory***, *PSAT median RT*[b]	0.0003	0.261	0.0001	0.001	0.007
Model 1 (adjusting for age, sex, and education)					
Model 2 (adjusting for age, sex, education, and kidney disease)	0.0003	0.219	0.00004	0.001	0.023
Model 3 (adjusting for age, sex, education, kidney disease, and glycemic variability)	0.0003	0.205	0.00003	0.001	0.028
Dependent variable: β-amyloid 42/40 (*n* = 109)					
Predictor:					
Verbal reasoning, *Vocabulary accuracy*[a,b]					
Model 1 (adjusting for age, sex, and education)	0.028	0.260	0.007	0.048	0.009
Model 2 (adjusting for age, sex, education, and kidney disease)	0.028	0.261	0.007	0.048	0.010
Model 3 (adjusting for age, sex, education, kidney disease, and age at diagnosis)	0.026	0.245	0.006	0.046	0.011
Dependent variable: GFAP (*n* = 102)					
Predictor:					
Working memory, *PSAT median RT*[b]					
Model 1(adjusting for age, sex and education)	0.0002	0.175	0.00001	0.0004	0.036
Model 2 (adjusting for age, sex, education, and kidney disease)	0.0002	0.159	0.00001	0.0004	0.062
Model 3: (adjusting for age, sex, education, kidney disease, and severe hypoglycemic events)	0.0002	0.185	0.00001	0.00042	0.042

Abbreviations: ATN, β-amyloid, tau pathology, and neurodegeneration; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; PSAT, Paced Serial Addition Test; pTau, phosphorylated tau; RT, reaction time.

[a]Vocabulary accuracy was the only predictor associated with the outcome in the model. Age was associated with pTau181 and GFAP. Kidney-related disease was associated with pTau181. Age at diagnosis was associated with β-amyloid 42/40. Data for pTau181, pTau217, GFAP, and NfL were log10 transformed in the regression models.

[b]Statistics reported in the table refer to the cognitive variable after adjusting for the other variables in each model.

eral population and is highly associated with the clinical presentation of dementia.[39] Future research is needed to understand whether concentrations of these different plasma biomarkers reflect specific neurodegenerative processes in adults with T1D.

Recently, studies on ATN plasma biomarkers showed that reduced renal function may affect plasma biomarker concentrations.[12,40,41] The presence of kidney disease has also been found to be a risk factor for vascular dementia and AD in some,[42,43] but not all studies.[44,45] We observed that pTau181, pTau217, and NfL, but not β-amyloid 42/40 ratio and GFAP, were significantly higher in those with kidney disease in this study. This is consistent with studies showing that biomarker ratios may be less affected by glomerular filtration,[14,46] which would be the case for β-amyloid 42/40. Similarly, a 17-year follow-up study with 6256 participants conducted in Germany found no association between GFAP and kidney function.[44] Here, we found that the presence of kidney disease, as determined by medical record review, only slightly altered the associations between plasma biomarkers and cognitive function. Interestingly, GFAP was one of the biomarkers that was not directly associated with the presence of kidney disease in this study. In addition, abnormal hepatic β-amyloid clearance has been associated with brain β-amyloid deposition.[47] Our sample has no cases of chronic liver disease. However, our findings are limited by not having a measure of kidney or liver function. Future work on the use of plasma biomarkers in individuals at risk for kidney disease should also include eGFR and CSF or imaging biomarkers to study the effects of reduced renal and liver function on the validity of ATN plasma biomarkers levels and establish concentration reference ranges.

All five ATN plasma biomarkers included in this study were associated with other diabetes-related characteristics, complications, and vascular risk factors. After adjustment, higher pTau181 concentrations

were associated with greater glycemic variability, higher pTau217 concentrations were associated with the presence of neuropathy, lower β-amyloid 42/40 ratios were associated with older age at T1D onset, and higher GFAP concentrations were associated with lifetime number of severe hypoglycemic events. As such, our results show that plasma biomarkers of neurodegeneration are associated with some diabetes characteristics in adults with T1D, and this may point to mechanisms that underly neurodegeneration in T1D. The association between lower β-amyloid 42/40 ratios and older age at T1D onset was not initially expected. One hypothesis is that, since those with T1D onset at younger ages have different cognitive profiles, with more impairment throughout life[1,48] and potentially different etiology, compared to those with late-onset T1D,[49] the mechanisms underlying early and late T1D may play a role in risk for cognitive decline and/or protection. Epigenetic lifestyle risk factors suspected to be related to late-onset T1D, such as weight gain and smoking,[1] may also be associated with AD. Interestingly, in a recent study reporting plasma biomarkers in individuals with T1D, the authors also found an association between severe hypoglycemic events and GFAP concentrations, but in the opposite direction.[9] Further studies are needed to understand the relationship between the occurrence of severe hypoglycemic events and the presence of neurodegenerative markers.

4.1 | Strengths and limitations

Our study has limitations. First, we did not collect eGFR, creatinine, or liver function tests for our participants to estimate kidney or liver function. Second, our sample was of modest size and consisted predominantly of non-Hispanic White individuals, limiting the generalizability of our findings. Third, the wide age range in our sample (18–84 years), may have underpowered our analyses, as ATN plasma biomarkers are less likely to be present in younger individuals. The wide age range may also influence digital cognitive performance, as older participants may have lower digital skills. However, the tests used in this study have been validated in many cohorts of older adults.[24,50] Fourth, the cognitive assessment was weighted to the cognitive dysfunction commonly seen in T1D, rather than traditional tasks of episodic memory, visual-spatial skill, and semantic memory, which are typically associated with AD. Among the strengths of this study are that it is the first study to (i) report plasma ATN biomarker results in individuals with T1D, (ii) consider the presence of comorbidities including kidney disease, and (iii) investigate associations between plasma biomarkers of neurodegeneration and digital cognitive assessments, which are alternatives to traditional neuropsychology testing.

5 | CONCLUSION

In adults with T1D, concentrations of plasma pTau181, pTau217, β-amyloid 42/40 ratio, GFAP, and NfL were correlated with cognitive function. Multivariate analyses revealed that pTau181, GFAP, and β-amyloid 42/40 were associated with cognitive performance. Slower working memory was related to higher pTau181 and GFAP, suggesting that this may be an early indicator of neurodegeneration in this population. Kidney disease only slightly altered the associations between plasma biomarkers and cognitive function in this study. The possible effect of renal function on this biomarker requires further study. Moreover, the positive association between β-amyloid 42/40 and vocabulary, a measure of crystallized cognitive ability, may suggest protective mechanisms related to cognitive reserve. Further investigation of plasma ATN biomarkers and longitudinal cognitive decline will be crucial for determining their utility in T1D clinical care.

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CONFLICT OF INTEREST STATEMENT

R.S.W. has participated in multicenter clinical trials, through her institution, sponsored by Tandem, Insulet, Eli Lilly, Diasome, Amgen, and MannKind, and received DexCom devices at reduced cost for use in clinical research. The other authors have no conflicts of interest to report. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

Data for the current study are available from the corresponding author upon reasonable request. Examples of cognitive tests administered in the study protocol may be accessed online: https://osf.io/preprints/psyarxiv/dcszr

CONSENT STATEMENT

Written informed consent was obtained from all participants.

REFERENCES

1. Norris JM, Johnson RK, Stene LC. Type 1 diabetes-early life origins and changing epidemiology. *Lancet Diabetes Endocrinol*. 2020;8(3):226-238. doi:10.1016/S2213-8587(19)30412-7
2. Frazier HN, Ghoweri AO, Anderson KL, Lin RL, Porter NM, Thibault O. Broadening the definition of brain insulin resistance in aging and Alzheimer's disease. *Exp Neurol*. 2019;313:79-87. doi:10.1016/j.expneurol.2018.12.007
3. Shalimova A, Graff B, Gąsecki D, et al. Cognitive dysfunction in type 1 diabetes mellitus. *J Clin Endocrinol Metab*. 2019;104(6):2239-2249. doi:10.1210/jc.2018-01315

4. Jacobson AM, Ryan CM, Cleary PA, et al. Biomedical risk factors for decreased cognitive functioning in type 1 diabetes: an 18-year follow-up of the Diabetes Control and Complications Trial (DCCT) cohort. *Diabetologia*. 2011;54(2):245-255. doi:10.1007/s00125-010-1883-9
5. Lacy ME, Gilsanz P, Karter AJ, Quesenberry CP, Pletcher MJ, Whitmer RA. Long-term glycemic control and dementia risk in type 1 diabetes. *Diabetes Care*. 2018;41(11):2339-2345. doi:10.2337/dc18-0073
6. Ouwens DM, van Duinkerken E, Schoonenboom SN, et al. Cerebrospinal fluid levels of Alzheimer's disease biomarkers in middle-aged patients with type 1 diabetes. *Diabetologia*. 2014;57(10):2208-2214. doi:10.1007/s00125-014-3333-6
7. Smolina K, Wotton CJ, Goldacre MJ. Risk of dementia in patients hospitalised with type 1 and type 2 diabetes in England, 1998-2011: a retrospective national record linkage cohort study. *Diabetologia*. 2015;58(5):942-950. doi:10.1007/s00125-015-3515-x
8. Beeri MS, Bendlin BB. The link between type 2 diabetes and dementia: from biomarkers to treatment. *Lancet Diabetes Endocrinol*. 2020;8(9):736-738. doi:10.1016/s2213-8587(20)30267-9
9. Karger AB, Nasrallah IM, Braffett BH, et al. Plasma biomarkers of brain injury and their association with brain MRI and cognition in type 1 diabetes. *Diabetes Care*. 2024;47(9):1530-1538. doi:10.2337/dc24-0229
10. Alcolea D, Beeri MS, Rojas JC, Gardner RC, Lleó A. Blood biomarkers in neurodegenerative diseases: implications for the clinical neurologist. *Neurology*. 2023;101(4):172-180. doi:10.1212/WNL.0000000000207193
11. Hansson O, Blennow K, Zetterberg H, Dage J. Blood biomarkers for Alzheimer's disease in clinical practice and trials. *Nat Aging*. 2023;3(5):506-519. doi:10.1038/s43587-023-00403-3
12. Mielke MM, Dage JL, Frank RD, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med*. 2022;28(7):1398-1405. doi:10.1038/s41591-022-01822-2
13. Balogun WG, Zetterberg H, Blennow K, Karikari TK. Plasma biomarkers for neurodegenerative disorders: ready for prime time? *Curr Opin Psychiatry*. 2023;36(2):112-118. doi:10.1097/YCO.0000000000000851
14. Janelidze S, Barthélemy NR, He Y, Bateman RJ, Hansson O. Mitigating the associations of kidney dysfunction with blood biomarkers of Alzheimer disease by using phosphorylated tau to total tau ratios. *JAMA Neurol*. 2023;80(5):516-522. doi:10.1001/jamaneurol.2023.0199
15. Zhang B, Zhang C, Wang Y, et al. Effect of renal function on the diagnostic performance of plasma biomarkers for Alzheimer's disease. *Front Aging Neurosci*. 2023;15:1150510. doi:10.3389/fnagi.2023.1150510
16. Thanapornsangsuth P, Ongphichetmetha T, Luechaipanit W, Hemachudha P, Hemachudha T. Elevation of plasma phosphorylated tau181 during neurological illnesses affecting consciousness and kidney dysfunction. *Alzheimers Dement*. 2022;14(1):e12358. doi:10.1002/dad2.12358
17. Wallace AS, Chang AR, Shin JI, et al. Obesity and chronic kidney disease in US adults with type 1 and type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2022;107(5):1247-1256. doi:10.1210/clinem/dgab927
18. Salem RM, Todd JN, Sandholm N, et al. Genome-wide association study of diabetic kidney disease highlights biology involved in glomerular basement membrane collagen. *J Am Soc Nephrol*. 2019;30(10):2000-2016. doi:10.1681/ASN.2019030218
19. Mascarenhas Fonseca L, Strong RW, Singh S, et al. Glycemic Variability and Fluctuations in Cognitive status in adults with type 1 diabetes (GluCog): observational study using ecological momentary assessment of cognition. *JMIR Diabetes*. 2023;8:e39750. doi:10.2196/39750
20. TestMyBrain.org. Test My Brain. Accessed October 15, 2024. https://testmybrain.org
21. D'Ardenne K, Savage CR, Small D, Vainik U, Stoeckel LE. Core neuropsychological measures for obesity and diabetes trials: initial report. *Front Psychol*. 2020;11:554127. doi:10.3389/fpsyg.2020.554127
22. Hartshorne JK, Germine LT. When does cognitive functioning peak? The asynchronous rise and fall of different cognitive abilities across the life span. *Psychol Sci*. 2015;26(4):433-443. doi:10.1177/0956797614567339
23. Chaytor NS, Barbosa-Leiker C, Germine LT, Fonseca LM, McPherson SM, Tuttle KR. Construct validity, ecological validity and acceptance of self-administered online neuropsychological assessment in adults. *Clin Neuropsychol*. 2021;35(1):148-164. doi:10.1080/13854046.2020.1811893
24. Singh S, Strong RW, Jung L, et al. The TestMyBrain digital neuropsychology toolkit: development and psychometric characteristics. *J Clin Exp Neuropsychol*. 2021;43(8):786-795. doi:10.1080/13803395.2021.2002269
25. Treviño M, Zhu X, Lu YY, et al. How do we measure attention? Using factor analysis to establish construct validity of neuropsychological tests. *Cogn Res Princ Implic*. 2021;6(1):51. doi:10.1186/s41235-021-00313-1
26. Ophir E, Nass C, Wagner AD. Cognitive control in media multitaskers. *Proc Natl Acad Sci U S A*. 2009;106(37):15583-15587. doi:10.1073/pnas.0903620106
27. Germine LT, Joormann J, Passell E, et al. Neurocognition after motor vehicle collision and adverse post-traumatic neuropsychiatric sequelae within 8 weeks: Initial findings from the AURORA study. *J Affect Disord*. 2022;298(Pt B):57-67. doi:10.1016/j.jad.2021.10.104
28. Singh S, Strong R, Xu I, et al. Ecological momentary assessment of cognition in clinical and community samples: reliability and validity study. *J Med Internet Res*. 2023;25:e45028. doi:10.2196/45028
29. Passell E, Strong RW, Rutter LA, et al. Cognitive test scores vary with choice of personal digital device. *Behav Res Methods*. 2021;53(6):2544-2557. doi:10.3758/s13428-021-01597-3
30. Segev N, Hornung LN, Tellez SE, et al. Continuous glucose monitoring in the intensive care unit following total pancreatectomy with islet autotransplantation in children: establishing accuracy of the Dexcom G6 model. *J Clin Med*. 2021;10(9):1893. doi:10.3390/jcm10091893
31. Andriuta D, Diouf M, Roussel M, Godefroy O. Is reaction time slowing an early sign of Alzheimer's disease? A meta-analysis. *Dement Geriatr Cogn Disord*. 2019;47(4-6):281-288. doi:10.1159/000500348
32. Kochan NA, Bunce D, Pont S, Crawford JD, Brodaty H, Sachdev PS. Reaction time measures predict incident dementia in community-living older adults: the Sydney Memory and Ageing Study. *Am J Geriatr Psychiatry*. 2016;24(3):221-231. doi:10.1016/j.jagp.2015.12.005
33. Chatterjee P, Pedrini S, Doecke JD, et al. Plasma Aβ42/40 ratio, p-tau181, GFAP, and NfL across the Alzheimer's disease continuum: a cross-sectional and longitudinal study in the AIBL cohort. *Alzheimers Dement*. 2023;19(4):1117-1134. doi:10.1002/alz.12724
34. Snowdon DA, Greiner LH, Markesbery WR. Linguistic ability in early life and the neuropathology of Alzheimer's disease and cerebrovascular disease. Findings from the Nun Study. *Ann N Y Acad Sci*. 2000;903:34-38.
35. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. 2012;11(11):1006-1012. doi:10.1016/S1474-4422(12)70191-6
36. Simrén J, Leuzy A, Karikari TK, et al. The diagnostic and prognostic capabilities of plasma biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2021;17(7):1145-1156. doi:10.1002/alz.12283
37. Guo Y, You J, Zhang Y, et al. Plasma proteomic profiles predict future dementia in healthy adults. *Nat Aging*. 2024;4(2):247-260. doi:10.1038/s43587-023-00565-0
38. Pereira JB, Janelidze S, Smith R, et al. Plasma GFAP is an early marker of amyloid-β but not tau pathology in Alzheimer's disease. *Brain*. 2021;144(11):3505-3516. doi:10.1093/brain/awab223

39. Coomans EM, Verberk IMW, Ossenkoppele R, et al. A head-to-head comparison between plasma ptau181 and tau pet along the Alzheimer's disease continuum. *J Nucl Med*. 2023;64(3):437-443. doi:10.2967/jnumed.122.264279
40. Ramanan VK, Graff-Radford J, Syrjanen J, et al. Association of plasma biomarkers of Alzheimer disease with cognition and medical comorbidities in a biracial cohort. *Neurology*. 2023;101(14):e1402-e1411. doi:10.1212/WNL.0000000000207675
41. Dittrich A, Ashton NJ, Zetterberg H, et al. Association of chronic kidney disease with plasma NfL and other biomarkers of neurodegeneration: the H70 Birth cohort study in Gothenburg. *Neurology*. 2023;101(3):e277-e288. doi:10.1212/WNL.0000000000207419
42. Singh-Manoux A, Oumarou-Ibrahim A, Machado-Fragua MD, et al. Association between kidney function and incidence of dementia: 10-year follow-up of the Whitehall II cohort study. *Age Ageing*. 2022;51(1):afab259. doi:10.1093/ageing/afab259
43. Xu H, Garcia-Ptacek S, Trevisan M, et al. Kidney function, kidney function decline, and the risk of dementia in older adults: a registry-based study. *Neurology*. 2021;96(24):e2956-e2965. doi:10.1212/WNL.0000000000012113
44. Stocker H, Beyer L, Trares K, et al. Association of kidney function with development of Alzheimer disease and other dementias and dementia-related blood biomarkers. *JAMA Netw Open*. 2023;6(1):e2252387. doi:10.1001/jamanetworkopen.2022.52387
45. Helmer C, Stengel B, Metzger M, et al. Chronic kidney disease, cognitive decline, and incident dementia: the 3C Study. *Neurology*. 2011;77(23):2043-2051. doi:10.1212/WNL.0b013e31823b4765
46. Pichet Binette A, Janelidze S, Cullen N, et al. Confounding factors of Alzheimer's disease plasma biomarkers and their impact on clinical performance. *Alzheimers Dement*. 2023;19(4):1403-1414. doi:10.1002/alz.12787
47. Cheng Y, He CY, Tian DY, et al. Physiological β-amyloid clearance by the liver and its therapeutic potential for Alzheimer's disease. *Acta Neuropathol*. 2023;145(6):717-731. doi:10.1007/s00401-023-02559-z
48. van Duinkerken E, Ryan CM. Diabetes mellitus in the young and the old: Effects on cognitive functioning across the life span. *Neurobiol Dis*. 2020;134:104608. doi:10.1016/j.nbd.2019.104608
49. Leslie RD, Evans-Molina C, Freund-Brown J, et al. Adult-onset type 1 diabetes: current understanding and challenges. *Diabetes Care*. 2021;44(11):2449-2456. doi:10.2337/dc21-0770
50. Riley E, Okabe H, Germine L, Wilmer J, Esterman M, DeGutis J. Gender differences in sustained attentional control relate to gender inequality across countries. *PLoS One*. 2016;11(11):e0165100. doi:10.1371/journal.pone.0165100

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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